Health Canada needs to act on laboratory-developed diagnostics

Holloway, Kelly, PhD; Miller, Fiona A, PhD; Rousseau, François, MD; Gutierrez, Alberto, PhD; Hogarth, Stuart, PhD.

CMAJ published September, 2019; Vol 191(39)

Correspondence to**:** Fiona Miller, fiona.miller@utoronto.ca

An international exposé of flawed regulations for medical implants prompted Canada's health minister to announce sweeping changes to the regulation of medical devices.[1] Yet an important subset of medical devices remains outside the purview of this regulatory overhaul: laboratory-developed tests. These devices are diagnostic tests produced by a company in its own clinical laboratories and marketed as commercial services to health care providers who send samples to those laboratories for analysis "in house." Some laboratory-developed tests may also be developed by public clinical laboratories and offered to local clients. The recent expansion of the molecular diagnostics industry has revealed weaknesses in the regulatory system for all laboratory developed tests. Such tests are not subject to Canada's statutory regulation of medical devices for safety and efficacy, but they are widely used in Canada's health care system. Absent regulation as medical devices, the only controls on test performance are laboratory regulation and accreditation, which are heterogeneous and sometimes flawed and do not necessarily include assessment of test validity, safety and efficacy. Regulators in Australia, the United States and Europe have made efforts to close this "gaping regulatory loophole,"[2] but Health Canada has not indicated that it plans to do the same. In the interests of the nation's health, it should.

Molecular diagnostics increasingly play a pivotal role in control of infectious disease, diagnosis of hereditary diseases and aspects of oncology. The global molecular diagnostics market was estimated to be worth US$7.3 billion in 2017.[3] In Canada, many molecular diagnostics are covered by provincial health plans: for example, Harmony and Panorama, noninvasive prenatal tests that screen for common fetal trisomies, are covered for high-risk pregnancies in Ontario, British Columbia and the Yukon. Oncotype Dx — which offers women with early-stage invasive breast cancer information about their likely response to chemotherapy and the chance of recurring cancer — is reimbursed in BC, Alberta, Saskatchewan, Ontario, Quebec and Newfoundland. But these three tests were neither evaluated nor approved by Health Canada.

Diagnostics developed as "test kits" and sold to laboratories, hospitals and clinics are considered to be in vitro diagnostics devices under Medical Devices Regulation in accordance with the federal *Food and Drugs Act*. They are subject to premarket review by Health Canada to evaluate evidence of their safety and efficacy. However, manufacturers can avoid this regulatory approval process by using the laboratory-developed test loophole. In the past, such tests were developed in specialized hospital laboratories; they were not regulated as medical devices and were distributed to patients as a health service. But growing commercial interest in molecular diagnostics calls this approach into question. Moreover, this regulatory loophole establishes a far-from-level playing field for test manufacturers, as some widely used tests that have been reviewed and approved by Health Canada, such as Prosigna's NanoString and Myriad's EndoPredict prognostic tests for early-stage breast cancer, compete on the Canadian market with tests that have bypassed such review, like Oncotype Dx.

The current laboratory regulatory system in Canada involves a mixture of public and private entities and operates with oversight from provincial governments, nongovernmental organizations and professional societies.[4,5] Laboratory regulations are aimed at the laboratories themselves — addressing laboratory environment, hiring of personnel, laboratory operation, accreditation and quality control — but no entity is formally responsible across Canada for independently evaluating the development, validity or adverse events of tests delivered by laboratories, unless they are marketed as test kits and reviewed by Health Canada (see Appendix 1, available at www.cmaj.ca/lookup/ suppl/doi:10.1503/cmaj.190550/-/DC1).

Although the highest laboratory accreditation standards are sometimes mandated,[6] most provinces and territories rely on voluntary standards that are unevenly applied, with little auditing and systematic testing to ensure quality (www.the globeandmail.com/life/health -and-fitness/what-we-should-learn -from-our-pathology-problems/ article1357271/). This lack of proper regulation, controls and quality management "has potentially jeopardized the delivery

of quality, safe, timely and appropriate care."[5] Indeed, several high-profile cases of diagnostic error in Canadian laboratories have resulted in patient harm[7] (www.cbc.ca/news/canada/motherisk-hair -testing-families-1.4360577).

Although some laboratory-developed tests have undergone careful review, with findings published in scientific journals or endorsed by clinical practice guidelines, others have not. Moreover, published evidence often excludes elements essential to the validation of such tests.[8] And there is no test registry. No one, including Health Canada, is keeping track.

Outside Canada, poor test quality and diagnostic error have drawn attention,[9] prompting several jurisdictions to address the regulatory weaknesses that contribute to these problems (Appendix 2, available at www.cmaj.ca/lookup/ suppl/doi:10.1503/cmaj.190550/-/DC1). Australia developed a light-touch approach starting in 2010, subjecting only the highest-risk laboratory-developed tests to external evaluation and tracking in a public registry.[10] For class I–III tests (lower risk), the system relies on standards for accreditation in compliance with the National Association of Testing Authorities, without registration in a public database.

The US began trying to regulate these tests more than 25 years ago; the US Food and Drug Administration (FDA) has exercised enforcement discretion in managing the industry, issuing warning and cease-and-desist letters in the face of particularly egregious behaviour, and proposed more comprehensive policy reform. In 2010, the FDA began considering a policy change so that all such tests would be regulated in the same manner as traditionally distributed in vitro diagnostics devices. In 2014, the FDA issued draft guidance to propose clear oversight of laboratory-developed tests, but this was withdrawn and replaced with a discussion paper before the 2016 presidential election. Most recently, a bipartisan bill has been drafted proposing a regulatory framework for all in vitro diagnostics,[11] yet its fate is currently unclear.

A new European Union (EU) regulation on in vitro diagnostics — passed in 2017 and due to be fully implemented by 2022 — will subject laboratory-developed tests manufactured on

an "industrial scale" to regulatory review. This approach targets commercial laboratories while permitting a "health institution exemption" with reduced but still substantial oversight for those tests that continue to be used within individual hospital laboratories. Under the new directive, the proportion of tests required to be submitted for approval will likely increase from 10% to 90%.

In April 2018, the Standards Council of Canada introduced a voluntary standard, in collaboration with the Medical Devices Bureau of Health Canada and partners from the clinical laboratory industry, Siemens and Roche, for laboratories developing tests. The standard acknowledges that "while many laboratories can perform validation studies of these tests, there is no standard by which to assess their performance, quality, and reliability."[12] It is similar to the Australian regulation, even referencing the Therapeutic Goods Administration when defining laboratory-developed tests. Yet Canada seems to be addressing the issue with a lighter touch than Australia by failing to regulate even high-risk tests or to track laboratory-developed tests in a public registry. The standard is merely a high-level document for laboratories to understand how they can voluntarily validate their tests, with much room for interpretation. It is an inadequate solution.

After the exposé on regulation of medical devices, which revealed how a flawed and secretive regulatory system caused debilitating injury and death, Canada responded with efforts to strengthen the regulatory process for premarket approval of medical devices, enhance postmarket surveillance and make the system more transparent. Before this, Canada also announced leading regulatory reform on transparency with new requirements for public dissemination of clinical data supporting approval of drugs and devices, including regulated in vitro diagnostics. In February 2019, Canada's Medical Devices Regulations were amended, giving Health Canada authority to publish "summaries and detailed information of all clinical studies and investigational testing that provided evidence of safety and effectiveness" for

class III and IV medical devices submitted to them for approval, starting in 2021.[13] This international leadership in data transparency contrasts starkly with Health Canada's inadequate regulation of laboratory-developed tests. Canada has an opportunity to draw from and build on regulatory advances in other countries, particularly the EU, to ensure the safety and effectiveness of these diagnostic products. The time to act is now.

References

1. Statement from the Minister of Health on the regulation of medical devices in Canada. Ottawa: Health Canada [statement]; 2018 Nov. 29. Available: www.canada. ca/en/health-canada/news/2018/11/statement-from-the-minister-of-health-on-the -regulation-of-medical-devices-in-canada.html (accessed 2019 Mar. 19).

2. Holloway K, Miller FA, Gutierrez A, et al. Dangerous diagnostics? Regulatory reform in the genomic era. *BMJ* 2019;364:l640.

3. Kalorama Information. The World Molecular Diagnostics Market — 7th edition (HIV testing, hepatitis testing, molecular cancer tests, blood screening, hospitalaAcquired tests, RSV, CT/NG, HPV, Inherited Diseases, ISH). Arlington (VA): BioInformatics Inc.; 2017 Jan. 30. Available: https://kaloramainformation.com/ product/the-world-molecular-diagnostics-market-7th-edition-hiv-testing -hepatitis-testing-molecular-cancer-tests-blood-screening-hospital-acquired -tests-rsv-ct-ng-hpv-inherited-diseases-ish/ (accessed 2019 Mar. 19).

4. Li H, Adeli K. Laboratory quality regulations and accreditation standards in Canada. *Clin Biochem* 2009;42:249-55.

5. Gamble B, Bourne L, Deber RB. Accountability through regulation in Ontario's medical laboratory sector. *Healthc Policy* 2014;10:67-78.

6. *Entente de partenariat entre le BNQ et le CQA pour l'agrément et l'accréditation des laboratoires de biologie médicale (LBM)*. Montréal: Bureau de normalisation du Québec; 2017 Apr. 27.

7. Cameron MA. *Commission of inquiry on hormone receptor testing*. St. John's: Government of Newfoundland and Labrador; 2009 Mar. 1.

8. Waerner T, Thurnher D, Krapfenbauer K. The role of laboratory medicine in healthcare: quality requirements of immunoassays, standardisation and data management in prospective medicine. *EPMA J* 2010;1:619-26.

9. National Academies of Sciences, Engineering, and Medicine. *Improving diagnosis in health care*. Washington (DC): The National Academies Press; 2015. Available: www.nationalacademies.org/hmd/Reports/2015/Improving -Diagnosis -in-Healthcare.aspx (accessed 2019 Mar. 29).

10. *Regulatory requirements for in-house IVDs: version 2.2*. Woden (Australia): Department of Health, Therapeutic Goods Administration, Australian Government; 2018. Available: www.tga.gov.au/publication/regulatory-requirements-house-ivds (accessed 2019 Mar. 19).

11. Verifying Accurate Leading-edge IVCT Development Act. Preliminary discussion draft. 115th congress, 2nd sess, 2018 Dec. 6. Available: www.genomeweb. com/sites/default/files/valid_act_discussion_draft_12.6.18.pdf (accessed 2019 Mar. 19).

12. Requirements for the design, development, and validation of laboratorydeveloped tests used for the screening, diagnosis, and management of clinical conditions. Toronto: Canadian Standards Assocoation; 2018.

13. Public release of clinical information: guidance document. Ottawa: Health Canada; modified 2019 Apr. 1. Available: www.canada.ca/en/health-canada/ services/drug-health-product-review-approval/profile-public-release-clinical -information-guidance/document.html#s2.3 (accessed 2019 Apr. 8).

Competing interests: Kelly Holloway's salary is paid by a Canadian Institutes of Health Research (CIHR) grant (PJT 148805) to investigate the issues reviewed in this paper. Fiona Miller is the principal investigator on the study funded by the same CIHR grant to investigate the issues reviewed in this paper. François Rousseau is a co-applicant on the same CIHR grant to investigate the issues reviewed in this paper and holds a salary award in evidence-based laboratory medicine from the Fonds de recherche du Québec–Santé, le Ministère de la santé du Québec and le CHU de Québec — Université Laval. Alberto Gutierrez is a partner at NDA Partners, which offers regulatory services for the biopharma industry. Dr. Gutierrez was also previously employed by the US Food and Drug Administration, regulating in vitro diagnostics. Stuart Hogarth is the principal investigator on a study funded by the European Research Council to investigate the issues reviewed in this paper. No other competing interests were declared. This article has been peer reviewed.

Affiliations: Institute of Health Policy, Management and Evaluation (Holloway, Miller), University of Toronto, Toronto, Ont.; Department of Molecular Biology, Medical Biochemistry and Pathology (Rousseau), Université Laval, Québec, Que.; NDA Partners, LLC (Gutierrez), Va.; Department of Sociology (Hogarth), University of Cambridge, Cambridge, UK

Contributors: All of the authors made substantial contributions to the conception and design of the work, and to the analysis and interpretation of the data. Kelly Holloway drafted the manuscript and all authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: Funded by an investigator-initiated grant to Fiona Miller, Kelly Holloway and François Rousseau from CIHR (PJT 148805). SH acknowledges funding from the European Research Council (Starting Grant: CANCERSCREEN Screening for cancer in the post-genomic era: diagnostic innovation and biomedicalisation in comparative perspective, grant agreement No

716689, PI SH). The funders had no role in the conceptualization and drafting of this paper or the decision to submit for publication.